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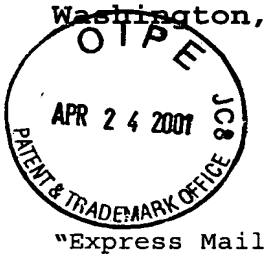

BOX PATENT EXTN

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I hereby certify that the following attached paper or fee

Letter dated April 24, 2001, Check for $1,120.00, Power, 37 CFR 3.73(b) Certificate, Letter to Dr. Bonnie Davis, copy Merck Index, Copy '318 patent, copy (3) Maintenance Statements; Three copies of the above, Postcard

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Director for Patents, Washington, D.C. 20231

HUGH R WOTHERSPOON
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(Signature of person mailing paper or fee)

Each paper, letter or communication relating to an international application during the international stage for which a date of filing is to be obtained as of the date of mailing must have its own certificate and the "Express Mail" label number as a part thereof or attached thereto. When, as here, the certification is presented on a separate sheet, that sheet must(1) be signed and (2) fully identify and be securely attached to the paper or fee it accompanies. Identification should include the serial number and filing date of the application as well as the type of paper being filed, e.g. complete application, specification and drawings, responses to rejection or refusal, notice of appeal, etc. If the serial number of the application not known, the identification should include at least the name of the inventor(s) and the title of the invention.

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April 24, 2001

Director of United States Patent and Trademark Office
Box **Patent Extension.**
Washington, D.C. 20231

Dear Sir:

Application for Extension of Patent Term of U.S. Patent 4,663,318 Pursuant to 35 U.S.C. Section 156 Extension of the Term of U.S. Patent 4,663,318 for a Term Expiring on December 12, 2008 is hereby requested for the reasons set out below:

Requirements Pursuant to 37 CFR 1.710

37 CFR 1.710(a) A patent is eligible for extension of the patent term if the patent claims a product as defined in paragraph (b) of this section, either alone or in combination with other ingredients that read on a composition that received permission for commercial marketing or use, or a method of using such a product ....

b) The term "A product referred to in paragraph (a) of this section means

1) The active ingredient of a new human drug, antibiotic drug ... (as those terms are used in the Federal Food, Drug and Cosmetic Act ....) including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient ...

U.S. Patent 4,663,318 in claim 1 thereof recites:

> "1. A method of treating Alzheimer's disease ... which comprises administering ... galanthamine or a pharmaceutically acceptable acid addition salt thereof".

Galantamine hydrobromide has received permission for commercial use under application number NDA 21-169 for the treatment of mild to moderate dementia of the Alzheimer's type. Therefore, U.S. Patent 4,663,318 is subject to extension of the patent term.

Requirements Pursuant to 37 CFR 1.720

37 CFR 1.720(a) The term of a patent may be extended if the patent claims a product or a method of using a product as defined in 37 CFR 1.710.

U.S. Patent 4,663,318 in claim 1 thereof recites:

> "A method of treating Alzheimer's disease ... which comprises administering ... galanthamine or a pharmaceutically acceptable acid addition salt thereof".

37 CFR 1.710 defines "a product" as "The active ingredient of a new human drug ... (as those terms are used in the Federal Food, Drug and Cosmetic Act ....") including any salt or ester of the active ingredient as a single entity or in combination with another active ingredient ..." Galantamine hydrobromide is the active ingredient which is found in the final dosage form prior to admininistration of the product to the patient for the drug "Reminyl®" which has received approval under application number

NDA 21-169. Thus, the U.S. '318 patent claims a method of using a product as defined in 37 CFR 1.710.

> ***37 CFR 1.720(b) The term of a patent may be extended if the term of the patent has never been previously extended except for extensions issued pursuant to sections 1.701, 1.760 and 1.790.***

U.S. Patent 4,663,318 has never been previously extended.

> ***37 CFR 1.720(c) The term of a patent may be extended if an application for extension is submitted in compliance with 37 CFR 1.740.***

We set out an explanation of how this application complies with 37 CFR 1.740 below.

> ***37 CFR 1.720(d) The term of a patent may be extended if the product has been subject to a regulatory view period as defined in 35 USC 156(g) before its commercial marketing or use.***

Galantamine hydrobromide (as "Reminyl®") has been subject to regulatory review under application number NDA 21-169. We set out below how the regulatory review period as defined in 35 USC 156(g) is calculated.

> ***37 CFR 1.720(e) The term of a patent may be extended if the product has received permission for commercial marketing or use and ... the permission for the commercial marketing or use of the product is the first received permission for commercial marketing or use under the provisions of***

law under which the applicable regulatory review occurred.

Galantamine hydrobromide has received permission for commercial use under application number NDA 21-169 for the treatment of mild to moderate dementia of the Alzheimer's type. This permission is the first received permission for galantamine hydrobromide for any use under the provisions of law under which the regulatory review occurred.

37 CFR 1.720(f) The term for patent may be extended if the application is submitted within the 60 day period beginning on the date the product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred.

We make this showing under 37 CFR 1.740(a)(5) below.

37 CFR 1.720(g) The term for patent may be extended if the term of the patent including any interim extension issued pursuant to section 1.790 has not expired before the submission of an application in compliance with 37 CFR 1.741.

U.S. Patent 4,663,318 issued on May 5, 1987. Pursuant to 35 USC 154(c)(1) ' The term of a patent that is in force on.....the date that is 6 months after the date of the enactment of the Uruguay Round Agreements shall be the greater of the 20 year term as provided in subsection (a), or 17 years from grant subject to any terminal disclaimers'. The

relevant 'Uruguay' date is June 8, 1995. The US '318 Patent was in force on June 8, 1995. The term of 17 years from May 5, 1987 is May 5, 2004. The date of expiration pursuant to 35 USC Section 154(a)(2) is 20 years from the U.S. filing date of January 15, 1986 **i.e. January 15, 2006**. The greater term is the term which expires on January 15 ,2006. Therefore, the term of the patent has not expired before the date hereof.

> ***37 CFR 1.720(h) The term of a patent may be extended if no other patent term has been extended for the same regulatory review period for the products.***

No other application apart from this application for patent term extension has been filed based on the regulatory review period referred to herein.

Requirements Pursuant to 37 CFR 1.730

Application is submitted in respect of U.S. Patent 4,663,318. The owner of record of the U.S. '318 patent is Synaptech Inc.(hereinafter referred to as 'Extension Applicant') of c/o Schwartz and Salomon, 42nd Floor, 225 Broadway, New York, NY 10007-3001. Extension Applicant is owner of record by virtue of an Assignment made between Intelligen Corporation of P.O. BOX 157, Cold Spring Harbor, N.Y. 11724, USA (hereinafter referred to as 'Intelligen') and Extension Applicant dated the 30th day of November 1995 of record at Reel 8376 Frames 0935-0943. Intelligen is the assignee of Bonnie Davis of 17 Seacrest Drive, Huntington, New York, 11743,USA(hereinafter referred to as 'Inventor') by

virtue of an assignment made between Inventor and Intelligen and dated July 26, 1990 of record at Reel 5392 Frames 428-430.

The marketing applicant pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act is Janssen Research Foundation (hereinafter referred to as "Marketing Applicant"). Marketing Applicant is a division of Janssen Pharmaceutica Inc., a Pennsylvania Corporation, which is a wholly owned subsidiary of Johnson and Johnson. Janssen Pharmaceutica NV a Belgian business corporation organized and existing under the laws of Belgium with its registered office at Turnhoutseweg 30,B-2340, Beerse, Belgium (hereinafter referred to as "Pharmaceutica") is Licensee of the patent pursuant to a License dated the 30th day of November, 1995 and made between Extension Applicant and Pharmaceutica. Pharmaceutica is also a wholly owned subsidiary of Johnson and Johnson. Thus, Marketing Applicant is related to Pharmaceutica (the Licensee of Extension Applicant) because each is a wholly owned subsidiary of Johnson and Johnson. Pharmaceutica is related to Extension Applicant through the License. The regulatory review period (the effective date of the IND permission) commenced on the 4th day of October, 1996 which is after the date of the License (November 30, 1995 (see above)). It can be seen that at all times during the regulatory review period there existed an agency relationship between Extension Applicant and Marketing Applicant.

All IND and NDA activities undertaken by Marketing Applicant, were carried out with the full and complete permission of Pharmaceutica and Johnson & Johnson. Extension Applicant attaches herewith a

letter dated the 19th day of April, 2001 from Marketing Applicant to Extension Applicant reciting that Extension Applicant is authorized to rely upon the activities of Marketing Applicant before the Regulatory Authority.

Requirements Pursuant to 37 CFR 1.740

37 CFR 1.740(a)(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is Galantamine hydrobromide(which may also be spelled Galanthamine hydrobromide). Galanthamine is listed in the Merck Index (Twelfth Edition) as compound 4357 (page 736). We enclose a copy of the entry. The Merck Index entry completely identifies Galanthamine. Galanthamine hydrobromide is the acid addition salt of Galanthamine.

37 CFR 1.740(a)(2) A complete identification of the federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review occurred pursuant to Section 505 subsections (b)and (i) of the Federal Food, Drug and Cosmetic Act.

37 CFR 1.740(a)(3) An identification of the date on which the product received permission for commercial marketing or use

under the provision of law under which the applicable regulatory review period occurred.

The product received permission for commercial use on the 28th day of February, 2001 (i.e. pursuant to a letter from the FDA to the Marketing Applicant with mailing date of 28th day of February, 2001).

37 CFR 1.740(a)(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, The Public Health Service Act or the Virus-Serum-Toxin Act or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) the use of which it was approved, and the provision of law under which it was approved.

The drug product contains a single active ingredient. The single active ingredient is Galantamine hydrobromide (see above). Pursuant to Approval Applicant's approval application the Galantamine hydrobromide was approved for use in the treatment of mild to moderate dementia of the Alzheimer's type. Galanthamine hydrobromide has not previously been approved for any commercial marketing or use under the statutes listed in 37 CFR 1.740(a)(4).

37 CFR 1.740(a)(5) A statement that the application is being submitted within the 60 day period permitted for submission pursuant to 37 CFR 1.720(f) and an indication of the date of the last day on which the application could be submitted.

Pursuant to 37 CFR 1.740(a)(3) (see above) the product received permission for commercial marketing or use on the 28th day of February, 2001. . The 60 day period pursuant to 37 CFR 1.720(f) expires on the 29th day of April, 2001. Therefore, the application is being submitted within the permitted period.

37 CFR 1.740(a)(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue and the date of expiration.

The patent is U.S. Patent Number 4,663,318. The inventor of U.S. '318 is Davis. The issuance date of U.S. '318 is May 5, 1987. The date of expiration of U.S. '318 pursuant to 35 USC Sections 154(a)(2)and 154 (c) is 20 years from the U.S. filing date of January 15, 1986 ***i.e. January 15, 2006***. In this regard please see our calculation set out under paragraph 37 CFR 1.720(g)above.

37 CFR 1.740(a)(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings.

We enclose a photocopy of U.S. Patent 4,663,318.

37 CFR 1.740(a)(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment or re-examination certificate issued in the patent.

There is no disclaimer. There is no certificate of correction. There is no re-examination certificate issued in the patent. We enclose photocopies of maintenance fee statements for the 'pay year 04' maintenance fee (statement mailed the 16th day of November 1990); for the 'pay year 08' maintenance fee (statement mailed the 5th day of October 1994); and for the 'pay year 12' maintenance fee (statement undated).

37 CFR 1.740(a)(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: ... (ii) The method of using the approved product if the listed claims include any claim to the method of using the improved product.

U.S. Patent 4,663,318 claims a method of using the approved product. The applicable patent claims are claims 1 and 4 in the U.S. '318 patent.

Claim 1 in U.S. Patent 4,663,318 recites:

"1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient

suffering from such a disease, a therapeutically effective amount of galanthamine or a pharmaceutically acceptable acid addition salt thereof".

The approved product is Galantamine hydrobromide in the tablet dosage form for the treatment of mild to moderate dementias of the Alzheimer's type. Galantamine hydrobromide is the acid addition salt of Galantamine. Therefore, claim 1 in U.S. Patent 4,663,318 reads on a method of using the approved product.

Claim 4 in U.S. Patent 4,663,318 recites:

"A method according to claim 1 where said administration is oral and is in the range 10-2000 mg per day."

The approval is for the tablet. Therefore, claim 4 also reads on a method of using the approved product.

37 CFR 1.740(a)(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 USC 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture as appropriate to determine the applicable regulatory view period as follows:
(i) For a patent claiming a human drug, antibiotic or human biological product (A) The effective date of the investigational new drug (IND) application and the IND number; (B) The date on which a new drug application (NDA) or a Product License

Application (PLA) was initially submitted and the NDA or PLA number and (C) The date on which the NDA was approved or the Product License issued.

Please go to new page 13.

Application for approval of the approved product was submitted under Investigational New Drug Application Number 51,538 having effective date October 4, 1996. Application for approval of the approved product was submitted under New Drug application (NDA) number NDA 21-169 which was initially submitted on the 29th day of September,1999. As set out in regard to 37 CFR 1.740(a)(3) (see above) NDA 21-169 was approved on the 28th day of February, 2001. (copy enclosed)

37 CFR 1.740(a)(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

Please go to new page 15.

Relevant Activities under IND 51,538

Date	Serial Number	From	Type	Details
9/5/1996	000	Janssen	Original IND	Original Investigational New Drug Application for REMINYL Tablets.
9/12/1996		FDA	Correspondence	Acknowledgement of receipt of the IND.
9/18/1996		FDA	Correspondence	Request CMC information
9/27/1996	001	Janssen	Information Amendment	Response to 9/18/1996 CMC information request.
10/4/1996		FDA	Phone	Initiation of Phase III study.
10/17/1996			FDA Meeting	End-of-Phase II meeting held for REMINYL Tablets.
12/2/1996	006	Janssen	Information Amendment	Submission of pharmacology/toxicology and clinical reports: N123642, N123643, and N121951.
3/12/1997		FDA	Correspondence	FDA comments and requests regarding IND 51,538.
3/26/1997	013	Janssen	General Correspondence	Initial response to FDA letter of 3/12/1997.
4/1/1997			FDA Meeting	Pre-NDA CMC Meeting held with FDA for REMINYL Tablets.
4/7/1997	014	Janssen	Protocol Amendment	Submission of New Protocol GAL-INT-2.
5/8/1997	016	Janssen	Response to FDA Request for Information	Response to FDA correspondence dated 3/12/1997.
7/23/1997	020	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-3.
8/15/1997	021	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-2.
8/21/1997	022	Janssen	Information Amendment	Submission of Janssen's proposal for conducting carcinogenicity bioassays for galantamine.
11/25/1997		FDA	Fax	Comments on carcinogenicity proposal submitted on 8/21/1997.
11/26/1997	031	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-5.
12/18/1997	033	Janssen	Information Amendment	Addendum to Janssen's proposal for carcinogenicity testing program submitted on 8/21/1997 in response to FDA comments of 11/25/1997.
2/4/1998	038	Janssen	Protocol Amendment	Submission of New Protocols GAL-USA-6 and GAL-USA-9.
3/5/1998		FDA	Correspondence	FDA comments on carcinogenicity proposal submitted on 12/18/1997.
4/20/1998	051	Janssen	Information Amendment	Submission of revised Investigator's Brochure in response to FDA correspondence of 3/12/1997.
5/8/1998	056	Janssen	Information Amendment	Submission of the following nonclinical study reports: N125607, N123841, N121459, N123701, and N123873.
7/2/1998	059	Janssen	Draft Protocol	Submission of Draft Protocol GAL-USA-10 and request for FDA comments.
7/29/1998		FDA	Correspondence	Comments on draft protocol (GAL-USA-10) submission of 7/2/1998.
8/20/1998	061	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-10.
10/9/1998		FDA	Phone	Information request from FDA Biopharmaceutics Reviewer.
10/13/1998			FDA Meeting	Pre-NDA Meeting held with FDA for REMINYL Tablets.

Date	Serial Number	From	Type	Details
10/23/1998	067	Janssen	Response to FDA Request for Information	Submission of information on galantamine metabolism in human, formulation links, and draft dissolution data in response to FDA request of 10/9/1998.
12/9/1998	074	Janssen	Information Amendment	Submission of the following toxicity studies: N130862, N130784, N137003, N130719, N130813, and N133672.
12/28/1998	076	Janssen	Information Amendment	Submission of the following toxicity studies: N137047 and N137048.
1/29/1999	083	Janssen	Correspondence	Submission of information regarding carcinogenicity assays for 2/3/1999 FDA teleconference.
2/3/1999			Teleconference	Galantamine carcinogenicity teleconference held with FDA.
2/4/1999	084	Janssen	General Correspondence	Type-A Meeting Request for REMINYL Tablets.
3/5/1999	092	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-11.
3/10/1999	093	Janssen	General Correspondence	Submission of Type-A Meeting (3/24/1999) pre-meeting package.
3/24/1999			FDA Meeting	Type-A Meeting held with FDA.
4/13/1999	102	Janssen	General Correspondence	Meeting request to discuss the natural to synthetic switch for galantamine.
4/22/1999	104	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-12.
5/6/1999		FDA	Correspondence	FDA comments on new protocol (GAL-USA-11) submission of 3/5/1999.
5/10/1999	108	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-16.
5/26/1999	112	Janssen	Information Amendment	Submission of the following toxicity studies: N133946, N133935, and N137197.
5/28/1999	113	Janssen	General Correspondence	Submission of meeting package for 6/16/1999 FDA meeting to discuss synthetic galantamine.
6/16/1999			FDA meeting	FDA meeting held to discuss synthetic galantamine.
6/28/1999	120	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-17.
6/30/1999	121	Janssen	General Correspondence	Response to FDA comments of 5/6/1999 regarding design of protocol GAL-USA-11.
7/2/1999	122	Janssen	Information Amendment	Submission of information amendment consisting of the Clinical Expert Report and Clinical Summary from the REMINYL International Registration File (N137430 and N137396).
7/26/1999	130	Janssen	General Correspondence	Provision of sample E-submission materials.
9/17/1999	144	Janssen	Information Amendment	Submission of CMC information amendment supporting the use of synthetic galantamine.
3/15/2000	165	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-18.
4/14/2000	170	Janssen	Response to FDA Request for Information	Identification of Norgalantamine structure.
6/14/2000			FDA Meeting	Type-B Meeting held with FDA.
7/7/2000	177	Janssen	Protocol Amendment	Submission of New Protocol GAL-USA-19.

Relevant Activities under NDA 21-169

Date	From	Type	Details
9/29/1999	Janssen	Original NDA	Original New Drug Application for REMINYL Tablets.
10/20/1999	FDA	Correspondence	Acknowledgement of receipt of the NDA.
11/1/1999	Janssen	Correspondence	Letter to authorize FDA to review galantamine DMF.
11/12/1999	Janssen	Amendment	Response to CMC information request of 11/1/1999.
11/23/1999	Janssen	Correspondence	Submission of adverse event information for GAL-USA-1, GAL-INT-1, and GAL-INT-2, per FDA request of 11/4/1999.
1/12/2000	FDA	Phone	Request from a Medical Reviewer for information pertaining to studies GAL-INT-1 and GAL-USA-1.
1/18/2000	FDA	Phone	Request from a Statistician for statistical programming information for studies GAL-USA-1, GAL-INT-1, GAL-INT-2 and 95-05.
1/21/2000	Janssen	Correspondence	Submission of information pertaining to studies GAL-INT-1 and GAL-USA-1 per FDA request of 1/12/2000.
1/27/2000	Janssen	Amendment	Submission of statistical programming information from studies GAL-USA-1, GAL-INT-1, GAL-INT-2, and 95-05, per FDA request of 1/18/2000.
2/8/2000	Janssen	Correspondence	Response to FDA request for information pertaining to PK Report N137314 on 2/3/2000.
2/18/2000	Janssen	Correspondence	Response to FDA request for information pertaining to PK Report N141967 on 2/18/2000; Submission of galantamine tablets dissolution data per FDA request of 2/8/2000.
2/25/2000	Janssen	Correspondence	Submission of galantamine tablets dissolution data from Lot 0150L following submission of 2/18/2000.
2/25/2000	Janssen	Amendment	Submission of additional safety and efficacy information for REMINYL Tablets.
3/21/2000	FDA	Information Request Letter	Request for CMC information pertaining to NDA 21-169.
4/10/2000	FDA	Phone	Divisional comments on potential approval timeframe; Use of MEDRA system for analyzing AEs; Fast track review for Lewy-Body Dementia indication.
4/18/2000	Janssen	Correspondence	Response to request for information of 4/18/2000.
4/19/2000	FDA	Fax	Receipt of FDA consultation response regarding acceptability of REMINYL trade name.
4/20/2000	Janssen	Amendment	Response to information request from a Medical Reviewer on 4/11/2000.
5/23/2000	Janssen	Phone	Potential nature/timing of action letter for REMINYL NDA.
5/25/2000	Janssen	Amendment	Response to FDA Information Request Letter (CMC) dated 3/21/2000.
6/8/2000	Janssen	Amendment	Response to information request from a Pharmacology/Toxicology Reviewer on 5/3/2000.
6/29/2000	FDA	Information Request Letter	Request for CMC information pertaining to NDA 21-169.
7/19/2000	Janssen	Amendment	Response to FDA Information Request Letter (CMC) dated 6/29/2000.
7/29/2000	FDA	Action Letter	FDA Approvable Action Letter for REMINYL Tablets.
8/3/2000	Janssen	Correspondence	Intention to file an amendment to 7/29/2000 Approvable Letter.
8/9/2000	FDA	Phone	Scheduling of teleconference to discuss FDA labeling modifications.

Date	From	Type	Details
8/15/2000		Teleconference	Teleconference held to discuss FDA's modifications to REMINYL labeling.
8/31/2000	Janssen	Amendment	Resubmission in response to 7/29/2000 Approvable Letter.
9/22/2000	FDA	Correspondence	Acknowledgement of receipt of 8/31/2000 resubmission (Assignment of Class 2 review status).
9/27/2000	Janssen	Correspondence	Appeal of FDA Classification of 8/31/2000 resubmission.
10/2/2000	Janssen	Amendment	Submission of adverse event information from study GAL-USA-11, per FDA request of 10/2/2000 from a Medical Reviewer.
10/12/2000	Janssen	Amendment	Response to information request from a Medical Reviewer on 10/2/2000.
12/01/2000	Janssen	Amendment	Response to information requests from a Medical Reviewer on 11/7/2000 and 11/8/2000.
12/5/2000	Janssen	Amendment	Response to information request from a Medical Reviewer on 11/14/2000.
1/17/2001	Janssen	Amendment	Response to information request from a Medical Reviewer on 12/18/2000.
1/18/2001	Janssen	Amendment	Response to information request from a Medical Reviewer on 1/8/2001.
1/23/2001	Janssen	Amendment	Response to information request from a Medical Reviewer on 1/12/2001.
1/30/2001	Janssen	Amendment	Response to information request from a Medical Reviewer on 1/23/2001.
2/6/2001	Janssen	Amendment	Submission of revised package labeling for REMINYL Tablets.
2/12/2001		Teleconference	Teleconference held to discuss final product labeling for REMINYL Tablets.
2/23/2001	Janssen	Fax	Request to DDMAC for comments regarding a proposed press release for REMINYL Tablets.
2/27/2001	FDA	Fax	DDMAC comments regarding proposed press release for REMINYL Tablets submitted 2/23/2001.
2/28/2001	FDA	Action Letter	Approval Letter for REMINYL Tablets.
3/20/2001	Janssen	Amendment	Submission of Final Printed Labeling (FPL) for approved NDA 21-169.

37 CFR 1.740(a)(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for extension and a statement as to the length of extension claimed including how the length of extension was determined.

Please go to new page 20.

Extension Applicant in its opinion is eligible for the requested extension of patent term. We are required to show our calculation of the length of extension claimed which is set out below.

> ***Calculation of patent term extension for a human drug, antibiotic drug, or human biological product pursuant to 37 CFR 1.775.***
>
> ***37 CFR 1.775(c) - the length of the regulatory review period ... is the sum of:***
>
> ***(1) The number of days in the period beginning on the date an exemption under subsection (i) of Section 505 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under Section 351 of the Public Health Service Act.***
>
> ***The length of the regulatory review period ... is the sum of ... [37 CFR 1.775(c)(1)] (see above) and***
>
> ***(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under .... subsection (b) of Section 505 ... of the Federal Food, Drug and Cosmetic Act and ending on the date such application was approved under such section.***

The effective date of the IND permission

under the provisions of Section 505(i) of the FFDCA was October 4, 1996. The NDA application under the provisions of Section 505(b) of the FFDCA was initially submitted on September 29, 1999. Thus, the number of days in the period beginning on the date an exemption under Section 505(i) of the FFDCA and ending on the date of the NDA was initially submitted (under Section 505(b) FFDCA) is 1089 days.

The NDA was initially submitted (under Section 505(b) of the FFDCA) on September 29, 1999. The application was approved under such section on February 28, 2001. The number of days in the period beginning on the date the application was initially submitted and ending on the date such application was approved is 518 days.

We calculate the length of the regulatory review period (to be determined by the Secretary of Health and Human Services) to be 1607 days (subject to an reductions pursuant to paragraphs (d)(1)(i) through (d)(1)(iii).

U.S. Patent 4,663,318 issued on May 5, 1987. Since there are no days in the periods of paragraphs (c)(1) and (c)(2) of 37 CFR 1.775 which were on or before the date on which the patent issued then there are no deductions under 37 CFR 1.775(d)(1)(i).

Extension Applicant is a small company. Small companies often rely on Licensees in order to secure marketing approval. Licensing arrangements take time. We believe that the record shows that there has been no lack of diligence. We believe there should be no deduction under 37 CFR 1.775(d)(1)(ii).

The deduction under 37 CFR 1.775(d)(1)(iii) is 544 days. Therefore, the extension under 37 CFR 1.775(d)(1) is 1063 days.

37 CFR 1.775(d)(2). As set out under 37 CFR 1.740(a)(6) (see above) the original term of the patent ends on January 15, 2006. Adding the number of days determined in paragraph (d)(1)of this section gives the 12th day of December, 2008.

37 CFR 1.775(d)(3). Adding 14 years to the date of approval of the application under ... subection (b) of Section 505 ... of the Federal Food, Drug and Cosmetic Act gives the 28th day of February, 2015.

37 CFR 1.775(d)(4). Selecting the earlier date of the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) (see above) gives the 12th day of December, 2008.

37 CFR 1.775(d)(5). Since the original patent was issued after September 24, 1984 (i.e. on May 5, 1987) then (pursuant to 37 CFR 1.775(d)(5)(i)) add five years to January 15, 2006 (the original expiration date) gives January 15, 2011.

Pursuant to 37 CFR 1.775(d)(5)(ii) select the earlier date from the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of 37 CFR 1.775 gives the 12th day of December, 2008.

It follows from the above calculation that the 14 year patent term limit(i.e. the limit of 35 USC 156(c)(3)) does not apply. Also the 2 or 3 year patent term extension limits of 35 USC 156(g)(6)(C) do not apply.

37 CFR 1.740(a)(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

37 CFR 1.740(a)(14) The prescribed fee for receiving and acting upon the application for extension (see section 1.20(j)).

Pursuant to 37 CFR 1.20(j)(1) the fee for extension of patent term for financial year 2001 is $1,120.00. We enclose our check.

In the event we have under paid/ over paid the required fee the office is hereby authorized to suitably debit/credit our Deposit Account Number 12-0425.

37 CFR 1.740(a)(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please direct inquiries and correspondence relating to this application for patent term extension to:

John Richards, Esq.
Ladas & Parry
26 West 61 Street
New York, New York 10023
Telephone Number (212) 708-1915
Fax Numbers(212) 246-8959 and
(212)246-8925

37 CFR 1.740(b) The application under this section must be accompanied by two additional copies of such application (for a total of three copies).

We enclose the required three copies.

Respectfully submitted,

JOHN RICHARDS
Ladas & Parry
26 West 61st Street
New York, N.Y. 10023
Telephone No.(212) 708-1915
Registration No. 31053

Enclosure list

Copy approval letter dated February 28, 2001 from the Food and Drug Administration to Janssen Research Foundation

Statement Under 37 CFR 3.73(b)

Power of Attorney

Copy letter dated April 19, 2001 from Janssen Research Foundation to Dr. Bonnie Davis

Page 736 The Merck Index

Soft copy U.S. Patent Number 4,663,318

3 Maintenance Fee Statements

DEPARTMENT OF HEA_ _H & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-169

Janssen Research Foundation
Attention: Charles LaPree
Assitant Director, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Mr. LaPree:

Please refer to your new drug application (NDA) dated September 29, 1999, received September 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reminyl® (galantamine hydrobromide) Tablets.

We acknowledge receipt of your submissions dated:

August 3, 2000	October 2, 2000	December 5, 2000	January 23, 2001
August 31, 2000	October 12, 2000	January 17, 2001	January 30, 2001
September 12, 2000	December 1, 2000	January 18, 2001	February 6, 2001

Your submission of August 31, 2000 constituted a complete response to our July 29, 2000 approvable action letter.

This new drug application provides for the use of Reminyl® (galantamine hydrobromide) Tablets for the treatment of mild to moderate dementia of the Alzheimer's type.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format*-NDAs (January 1999).

For administrative purposes, this submission should be designated "FPL for approved NDA 21-169." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated August 31, 2001, to provide the histopathological examinations on cervices of all animals in the rat carcinogenicity study.

Reference is made to your correspondence submitted within this NDA, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Reminyl® for the treatment of mild to moderate dementia of the Alzheimer's type for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Melina Fanari, R. Ph, Regulatory Management Officer, at (301) 594-5526.

Sincerely,

(See appended electronic signature page)

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Robert Temple
2/28/01 03:31:16 PM

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000140

75M7/1005

LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

DATE MAILED
10/05/94

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,663,318	184	1870	----	06/819,141	05/05/87	01/15/86	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

EL 728212517 US

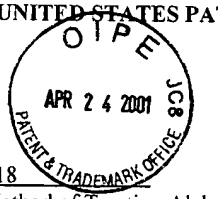
ITM NBR	ATTY DKT NUMBER
1	U 5631

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231**

Practitioner's Docket No. NPSP 010231 (HW) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Application No.: Group No.:
Filed: Examiner:
For:



Patent No.* : 4,663,318 Issue Date: May 5, 1987
Title: Method of Treating Alzheimer's Disease.
Inventor: Bonnie Davis.
Reexamination No.: _____ Issue Date: _____
Reissue: _____ Issue Date: _____
*NOTE: Insert name(s) of inventor(s) and title for patent.

RECEIVED
MAY 02 2001
OFFICE OF PETITIONS

Assistant Commissioner for Patents
Washington, D.C. 20231

STATEMENT UNDER 37 C.F.R. § 3.73(b) ESTABLISHING RIGHT OF ASSIGNEE TO TAKE ACTION

NOTE: *37 CFR 3.73(b) states: "When an assignee seeks to take action in a matter before the Office with respect to a patent application, ..., patent, registration, or reexamination proceeding, the assignee must establish its ownership of the property to the satisfaction of the Commissioner. Ownership is established by submitting to the Office, in the Office file related to the matter in which action is sought to be taken, documentary evidence of a chain of title from the original owner to the assignee (e.g., copy of an executed assignment submitted for recording) or by specifying (e.g., reel and frame number) where such evidence is recorded in the Office. The submission establishing ownership must be signed by a party authorized to act on behalf of the assignee. Documents submitted to establish ownership may be required to be recorded as a condition to permitting the assignee to take action in a matter pending before the Office."*

CERTIFICATION UNDER 37 C.F.R. 1.8(a) and 1.10*
*(When using Express Mail, the Express Mail label number is **mandatory**; Express Mail certification is optional.)*

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

☒ deposited with the United States Postal Service in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

37 C.F.R. 1.8(a)

with sufficient postage as first class mail.

37 C.F.R. 1.10*

(x) as "Express Mail Post Office to Address" Mailing Label No. EL 728212517US (mandatory)

TRANSMISSION

☐ transmitted by facsimile to the Patent and Trademark Office.

Date: April 24 2001

Maria Melian
Signature

Maria Melian
(type or print name of person certifying)

***WARNING:** *Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

EL 728212517US

NOTE: "Section 3.73(b) is amended to remove the sentence requiring an assignee to specifically state that the evidentiary documents have been reviewed and to certify that title is in the assignee seeking to take action. The sentence is deemed to be unnecessary in view of the amendment to §§ 1.4(d) and 10.18." Notice of Oct. 10, 1997, 62 Fed. Reg. 53,131, at 53,174.

1. The assignee(s) of the entire right, title and interest hereby seek(s) to take action in the PTO in this matter.

IDENTIFICATION OF ASSIGNEE

2. SYNAPTECH INC , of c/o Schwartz & Salomon, 225 Broadway, 42nd Fl, NewYork , NY 10007-3001

Name of assignee

Corporation

Type of assignee, e.g., corporation, partnership, university, government agency, etc.

NOTE: The Notice of April 30, 1993 (1150 O.G. 62-64) points out:

"The statement under 37 CFR 3.73(b) may be signed on behalf of the assignee in the following two manners if the assignee is an organization (e.g., corporation, partnership, university, government agency, etc.).

"(1) The statement may be signed by a person in the organization having apparent authority to sign on behalf of the organization. An officer (president, vice-president, secretary, or treasurer) is presumed to have authority to sign on behalf of the organization. The signature of the chairman of the board of directors is acceptable, but not the signature of an individual director. A person having a title (manager, director, administrator, general counsel) that does not clearly set forth that person as an officer of the assignee is not presumed to be an officer of the assignee or to have authority to sign the statement on behalf of the assignee. A power of attorney from the inventors in an organization to a practitioner to prosecute a patent application does not make the practitioner an official of an assignee or empower the practitioner to sign the statement on behalf of the assignee.

"(2) The statement may be signed by any person, if the statement includes an averment that the person is empowered to sign the statement on behalf of the assignee and, if not signed by a registered practitioner, the statement must be in oath or declaration form. Where a statement does not include such an averment, and the person signing does not hold a position in the organization that would give rise to a presumption that the person is empowered to sign the statement on behalf of the assignee, evidence of the person's authority to sign will be required."

(complete the following, if applicable)

(X) I, the person signing below, state that I am empowered to sign this statement on behalf of the assignee.I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

BASIS OF ASSIGNEE'S INTEREST

Ownership by the assignee is established as follows:

A.

1. ☐ An assignment from the inventor(s) of the matter identified above, which

was recorded in the PTO at
Reel_____ Frame_____

Practitioner's Docket No. NPSP 010231(HW)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

☐ In re application of:
Application No.: Group No.:
Filed: Examiner:
For:

(X) Patent No.*: 4,663,318 Issued: May 5, 1987
Title: Method of treating
Alzheimer's disease.
Inventor: Bonnie Davis.

**NOTE: Insert name(s) of all inventor(s) and title also for patent.*

Assistant Commissioner for Patents
Washington, D.C. 20231

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST
(REVOCATION OF PRIOR POWERS)

As assignee of record of the entire interest of the above identified

☐ application,

(X) patent,

REVOCATION OF PRIOR POWERS OF ATTORNEY

all powers of attorney previously given are hereby revoked and

NEW POWER OF ATTORNEY

the following attorney(s) and/or agent(s) are hereby appointed to prosecute and transact all business in the Patent and Trademark Office connected therewith.

JOSEPH H. HANDELMAN, 26179	JULIAN H. COHEN, 20302
JOHN RICHARDS, 31053	WILLIAM R. EVANS 25858
RICHARD J. STREIT, 25765	JANET I. CORD, 33778
PETER D. GALLOWAY, 27885	CLIFFORD J. MASS, 30086
IAIN C. BAILLIE, 24090	CYNTHIA R. MILLER, 34678
RICHARD P. BERG, 28145	

EL 728212517 US

SEND CORRESPONDENCE TO:

Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

DIRECT TELEPHONE CALLS TO:
(Name and telephone number)

(212) 708-1915

Optional Customer No. Bar Code

00140
00140
PATENT TRADEMARK OFFICE

Synaptech Inc
(type or print identity of assignee of entire interest)

c/o Schwartz and Salomon, 225 Broadway, 42nd Fl.
Address

New York, N.Y. 10007-3001

(X) Recorded in PTO on 02/12/96
Reel 8376
Frame 0943

☐ Recorded herewith

ASSIGNEE STATEMENT

Attached to this power is a "STATEMENT UNDER 37 C.F.R. section 3.73(b)."

(X) Bonnie h l.
Signature

Date: THIS 6th DAY OF APRIL 2001

(X) BONNIE DAVIS M.D.
(type or print name of person authorized to sign on behalf of assignee)

(X) SCIENTIFIC DIRECTOR.
Title

NOTE: The assignee of the entire interest may revoke previous powers and be represented by an attorney of his or her selection. 37 C.F.R. 1.36.

(check the following item, if it forms a part of this power of attorney)

☐ Added page—Authorization of attorney(s) to accept and follow instructions from representative.

2. ☐ An assignment (document) separately being submitted for recordal herewith.

AND/OR

B. (x) A chain of title from the inventor(s) to the current assignee as shown below:

1. From: Bonnie Davis
   Name of inventor(s)
   To: Intelligen Corporation of P.O. Box 157, Cold Spring Harbor, New York, 11724
   Recorded in PTO: Reel 5392, Frame 428—430

2. From: Intelligen Corporation (address as above)
   Name of inventor(s) or assignee
   To: Synaptech Inc, c/o Schwartz & Saloman, 225 Broadway, 42nd Floor, New York, NY 10007-3001
   Recorded in PTO: Reel 8376, Frame 0935-0943

3. From: _____
   Name of inventor(s) or assignee
   To: _____
   Recorded in PTO: Reel _____, Frame _____

(check item below, and add details, if applicable)

☐ Additional documents in the chain of title are listed in the attached Supplemental Sheet.

COPIES OF DOCUMENTS IN CHAIN OF TITLE

(complete this item, if copies are being sent)

☒ Copies of the assignment(s) or other document(s) in the chain of title are attached as follows:

☐	A	☐	1	☐	2		
(x)	B	(x)	1	(x)	2	☐	3

(X) April 6th, 2001
date

Bonnie Davis
Signature of authorized person

Bonnie Davis M.D.
(type or print name of authorized person)

Scientific Director
Title of authorized person

Reg. No.:

Tel. No.: ( )

Customer No.:

SIGNATURE OF PRACTITIONER

(type or print name of practitioner)

P.O. Address

c/o Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

80-518 U5631

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

☐ In re application of*: Bonnie Davis
Serial No.: 06/819,141 Group No. 125
Filed: May 15, 1986 Examiner: Friedman
For*: METHOD OF TREATING ALZHEIMER'S DISEASE

☒ Patent: 4,663,318 Issued: May 5, 1987

*NOTE: Insert name(s) of inventor(s) and title also for patent. Where recordal is with respect to a maintenance fee payment also insert application serial number and filing date and add Box M. Fee to Express

Commissioner of Patents and Trademarks
Washington, D.C. 20231

RECORDAL OF ASSIGNMENT (37 CFR 1.331)

1. Kindly record the enclosed assignment for the above identified
   - ☐ application
   - ☒ patent
2. When recordal has been effected, please return the original assignment document to the undersigned.
3. Fee Payment (37 CFR 1.21(h))
   - ☒ Attached is a check in the sum of $8.00.
   - ☐ Charge Account No. _____ the sum of $8.00. A duplicate of this recordal request is attached.

NOTE: 37 CFR 1.21(h). For recording each assignment, agreement or other paper relating to the property in a patent or application, per property, $8.00.

SIGNATURE OF ATTORNEY

Type or print name of attorney

P.O. Address

Tel. No. ( )
JOHN RICHARDS
Reg. No. c/o LADAS & PARRY
26 WEST 61st STREET
NEW YORK, N.Y. 10023
Reg. No. 31053 (212) 708-1915

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

JOHN RICHARDS
(Type or print name of person mailing paper)

Date 1 August 90

(Signature of person mailing paper)

91520292

(Recordal of Assignment (10-5))

U 5631

PATENT

For: ☐ U.S. and/or ☐ Foreign Rights
For: ☐ U.S. Application or ☒ U.S. Patent
By: ☐ Inventor(s) or ☒ Present Owner

ASSIGNMENT OF INVENTION

In consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration,

ASSIGNOR: (inventor(s) or person(s) or entity(ies) who own the invention)

Bonnie DAVIS
(Type or print name(s) of ASSIGNOR(S))

17 SEACREST DRIVE
HUNTINGTON, NEW YORK 11743
Address

U.S.S.A.
Nationality

(If assignment is by person or entity to whom invention was previously assigned and this was recorded in PTO add the following)

Recorded on ______
Reel ______
Frame ______

hereby sells, assigns and transfers to

ASSIGNEE:

INTELLIGEN CORPORATION
(Type or print name of ASSIGNEE)

P.O. Box 157
Address
COLD SPRING HALBOR NEW YORK 11724

______
Nationality

and the successors, assigns and legal representatives of the ASSIGNEE

(complete one of the following)

☒ the entire right, title and interest
☐ an undivided ______ percent (____%) interest

for the United States and its territorial possessions

(check the following box if foreign rights are also to be assigned)

☐ and in all foreign countries, including all rights to claim priority,

in and to any and all improvements which are disclosed in the invention entitled:

METHOD OF TREATING ALZHEIMER'S DESEASE

(check and complete (a), (b), (c) or (d))

and which is found in

(Assignment of Invention [16-3]—page 1 of 2)

REEL 5392 FRAME 429

RECORDED
PATENT AND TRADEMARK
OFFICE

AUG - 3 1990

(a) ☐ U.S. patent application executed on even date herewith

(b) ☐ U.S. patent application executed on _____

(c) ☐ U.S. application serial no. 0 /_____ filed on _____

(d) ☒ U.S. patent no. 4,663,318 issued MAY 5, 1987

(also check (a) if foreign application(s) is also being assigned)

(e) ☐ and any legal equivalent thereof in a foreign country, including the right to claim priority

and, in and to, all Letters Patent to be obtained for said invention by the above application or any continuation, division, renewal, or substitute thereof, and as to letters patent any reissue or re-examination thereof.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention and said Letters Patent and legal equivalents as may be known and accessible to ASSIGNOR and will testify as to the same in any interference, litigation or proceeding related thereto and will promptly execute and deliver to ASSIGNEE or its legal representatives any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this

X July 26, 1990 (Date of signing).

WARNING: Date of signing must be the same as the date of execution of the application if item (a) was checked above.

X Bonnie Davis

Signature of ASSIGNOR(S) Bonnie DAVIS

If ASSIGNOR is a legal entity complete the following information

_____

Type or print the name of the above person authorized to sign on behalf of ASSIGNOR

_____

Title

NOTE: No witnessing, notarization or legalization is necessary. If the assignment is notarized or legalized then it will only be prima facie evidence of execution 35 USC 261. Use next page if notarization is desired.

☐ Notarization or Legalization Page Added.

07-17-1996

102233540

Attorney's Docket No. U 3031-0 SPU 4295

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Assignments
Commissioner of Patents and Trademarks
Washington, D.C. 20231

NOTE: "Documents and cover sheets to be recorded should be addressed to Commissioner of Patents and Trademarks, Box Assignments, Washington, D.C. 20231, unless they are filed together with new applications or with a petition under § 3.81(b)." 37 CFR 3.27.

ASSIGNMENT (DOCUMENT) COVER SHEET (37 CFR 3.31)

NOTE: "A cover sheet may not refer to both patents and trademarks." 37 CFR 3.31(b).

Attached please find an assignment (document) for recordal.

CERTIFICATION 37 CFR 1.8(a) and 1.10

I hereby certify that this correspondence is, on the date shown below, being:

MAILING

☑ deposited with the United States Postal Service in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

37 CFR 1.8(a)

☑ with sufficient postage as first class mail.

37 CFR 1.10

☐ as "Express Mail Post Office to Addressee" Mailing Label No. _____

TRANSMISSION

☐ transmitted by facsimile to the Patent and Trademark Office.

_____
Signature

Date: February 8, 1996

John Richards
(type or print name of person certifying)

(Assignment (Document) Cover Sheet [16-6] —page 1 of 6)

IDENTIFICATION OF APPLICATION(S) AND/OR PATENT(S) FOR ASSIGNMENT (DOCUMENT) RECORDAL (37 CFR 3.21 and 37 CFR 3.31(c)(4))

NOTE: "An assignment relating to a patent must identify the patent by the patent number. An assignment relating to a national patent application must identify the national patent application by the application number (consisting of the series code and the serial number, e.g., 07/123,456) or the serial number and the filing date. An assignment relating to an international patent application which designates the United States of America must identify the international application by the international application number (e.g., PCT/US90/01234)." 37 CFR 3.21.

NOTE: § 3.21 does not apply to documents other than assignments. Notice of June 24, 1992 (1140 O.G. 63-72 at 67).

1. This assignment is for the following patent application and/or issued patent:

National application: SN: 0 / 819,141 filed on January 15, 1986

Provisional application: / filed on

International application: PCT/ /

Patent No. 4,663,318 Issued: May 5, 1987

(complete if applicable) which was previously assigned and recorded

Date _____ Reel _____

Frame _____

(also complete the following, if applicable)

☐ and also for the applications and/or patents shown on the attached list of FURTHER APPLICATION(S) and/or PATENT(S) BEING ASSIGNED

Number of pages added _____

NOTE: "Where there is a listing of properties contained within a document, any listing may be copied and attached to the cover sheet to reduce the amount of typing necessary. A notation of this attachment can be made in lieu of entering every property identification number on the cover sheet. Notice of June 24, 1992 (1140 O.G. 63-72 at 67).

TOTAL NUMBER OF APPLICATIONS AND/OR PATENTS AND TOTAL FEE (37 CFR 3.28(a)(6))

2. A. The total number of applications and/or patents identified in this cover sheet is

1

B. The total fee is (37 CFR 1.21(h)):

1 × $40.00 = $ 40.00

Total number of applications and/or patents

C. Payment of fee is made by:

☒ the attached check for $ 40.00

☐ Please charge Account _____

the sum of $ _____

A duplicate of this cover sheet is attached.

Please charge Account 12-0425 for any fee deficiency or credit to account any overpayment.

NAME OF PARTY(IES) CONVEYING INTEREST (37 CFR 3.31(a)(1))

NOTE: "The term 'party' as used in this rule [§ 3.31] means the person whose name appears on the documents to be recorded, that person's attorney or registered agent, or a corporate officer where a corporation's name appears on the documents." Notice of June 24, 1992 (1140 O.G. 53-72, at 65).

3. The party(ies) conveying interest is (are):

Name 1: Intelligen Corporation

Name 2:

Name 3:

NAME AND ADDRESS OF PARTY(IES) RECEIVING INTEREST (37 CFR 3.31(a)(2))

4. The rights are being conveyed to:

Name: Synopsech Inc.

Address: c/o Schwartz & Salomon
225 Broadway, 42nd Floor
New York, NY 10007-3001

DESCRIPTION OF INTEREST CONVEYED OR TRANSACTION RECORDED (37 CFR 3.31(a)(3))

5. The accompanying document intends to accomplish:

- [x] an assignment.
- [ ] a security agreement.
- [ ] a merger.
- [ ] a license
- [ ] a change of name.
- [ ] a change of address.
- [ ] other:

NAME AND ADDRESS OF PARTY TO WHOM CORRESPONDENCE SHOULD BE MAILED (37 CFR 3.31(a)(5))

6. Please address correspondence to:

Name: John Richards c/o Ladas & Parry
Address: 26 West 61 Street
New York, NY 10023
Telephone No.: (212) 708-1915

DATE ASSIGNMENT (DOCUMENT) EXECUTED (37 CFR 3.31(a)(7))

7. The attached assignment (document) was executed on November 30, 1995.
(date)

LANGUAGE OF ASSIGNMENT (DOCUMENT) TO BE RECORDED

NOTE: "The Office will accept and record non-English language documents only if accompanied by a verified English translation signed by the individual making the translation." 37 CFR 3.26.

8. The attached document:

- [x] is in the English language.
- [ ] is not in the English language and a verified English translation signed by the individual making the translation is attached.

ORIGINAL DOCUMENT OR TRUE COPY SUBMITTED

NOTE: "Either the original document or a true copy of the original document may be submitted for recording. Only one side of each page shall be used. The paper used should be flexible, strong, white, non-shiny, durable, and preferably no larger than 21.6 x 33.1 cm. (8 1/2 x 14 inches) with a 2.5 cm (one-inch) margin on all sides." 37 CFR 3.24.

9. Submitted herewith is:

☒ the original document.

☐ a true copy of the original document.

NOTE: "If the original [assignment] document is two-sided or the wrong size, the practitioner can comply with the requirement [set out in 37 C.F.R. § 3.24] by providing a true copy of the original document using only one side of each page on the correct size paper." Notice of June 24, 1992, 1140 O.G. 63-76, at 67.

ASSIGNMENT (DOCUMENT) TO RECORD CHANGE OF ADDRESS

(check item, if applicable)

10. ☐ Because the purpose of the attached documents is to record a change of address of the assignee, the particulars of the previously recorded assignments for each application and/or patent are shown.

ASSIGNMENT (DOCUMENT) TO RECORD CHANGE OF NAME

(check item, if applicable)

11 ☐ Because the purpose of the attached documents is to record a change of name of the assignee, the particulars of the previously recorded assignments for each application and/or patent are shown.

CHANGE OF PATENT MAINTENANCE FEE ADDRESS

(check item, if applicable)

12. ☐ A change of address to which correspondence is to be sent regarding patent maintenance fees is being sent to the Office separately.

STATEMENT (37 CFR 3.31(a)(9)) AND SIGNATURE (37 CFR 3.31(a)(10))

13. To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

NOTE: "The term 'party' as used in this rule [§ 3.31] means the person whose name appears on the documents to be recorded, that person's attorney or registered agent, or a corporate officer where a corporation's name appears on the document." Notice of June 24, 1992, 1140 O.G. 63-76, at 63.

Date: February 8, 1996

John Richards
Name of party submitting document

Signature of party submitting document

(complete the following, if the party submitting the document is applicant's attorney)

SIGNATURE OF ATTORNEY

Reg. No.

JOHN RICHARDS
c/o LADAS & PARRY
(type or print name of attorney) 26 WEST 61st STREET
NEW YORK, N.Y. 10023
Tel. No. ( ) Reg. No. 31053 (212) 708-1915

P.O. Address

TOTAL NUMBER OF PAGES BEING SUBMITTED

14. The total number of pages being submitted, including cover sheet attachment(s), and documents are:

9
Total number of pages submitted

Attorney's Docket No. _____ **PATENT**

For: ☒ U.S. and/or ☐ Foreign Rights
For: ☒ U.S. Application: or ☐ U.S. Patent
For: ☐ PCT Application:
By: ☐ Inventor(s) or ☐ Present Owner

ASSIGNMENT OF INVENTION

In consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration,

ASSIGNOR:

(inventor(s) or person(s) or entity(ies) who own the invention)

INTELLIGEN CORPORATION
(type or print name(s) of ASSIGNOR(S))
P.O. BOX 157
(Address)
COLD SPRING HARBOR, N.Y. 11724

USA
(Nationality)

(If assignment is by person or entity to whom invention was previously assigned and this was recorded in PTO, add the following)

Recorded on _____
Reel _____
Frame _____

hereby sells, assigns and transfers to

ASSIGNEE:

SYNAPTECH INC.
(type or print name(s) of ASSIGNOR(S))
C/O SCHWARTZ & SALOMON - 42nd FL.
225 BROADWAY
(Address)
NEW YORK, N.Y. 10007-3001

USA
(Nationality)

and the successors, assigns and legal representatives of the ASSIGNEE

(complete one of the following)

☒ the entire right, title and interest

☐ an undivided _____ percent (_____%) interest

for the United States and its territorial possessions

(check the following box if foreign rights are also to be assigned)

☐ and in all foreign countries, including all rights to claim priority,

in and to any and all improvements which are disclosed in the invention entitled:

METHOD OF TREATING ALZHEIMER'S DISEASE

(check and complete (a), (b), (c) or (d))

and which is found in

(a) ☐ U.S. patent application executed on even date herewith

(b) ☐ U.S. patent application executed on _____

☐ To comply with 37 CFR 3.21 for recordal of this assignment, I, an ASSIGNOR signing below, hereby authorize and request my attorney, as named in the Declaration and Power of Attorney I executed for this invention on the execution date stated above, to insert below the filing date and application number when it becomes known.

(c) ☒ U.S. application serial no. 0 / 819,141 filed on January 15, 1986

(d) ☐ International application no. PCT/_____/_____

(e) ☒ U.S. patent no. 4,663,318 issued May 5, 1987

☐ A change of address to which correspondence is to be sent regarding patent maintenance fees is being sent separately.

(also check (a) if foreign application(s) is also being assigned)

(f) ☐ and any legal equivalent thereof in a foreign country, including the right to claim priority

and, in and to, all Letters Patent to be obtained for said invention by the above application or any continuation, division, renewal, or substitute thereof, and as to letters patent any reissue or re-examination thereof

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention and said Letters Patent and legal equivalents as may be known and accessible to ASSIGNOR and will testify as to the same in any interference, litigation or proceeding related thereto and will promptly execute and deliver to ASSIGNEE or its legal representatives any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this
30th day of November 1995 (Date of signing).

WARNING: Date of signing must be the same as the date of execution of the application if item (a) was checked above.

Bennie Dav

Signature of ASSIGNOR(S)

If ASSIGNOR is a legal entity complete the following information

Bennie M Davis MD

(type or print the name of the above person authorized to sign on behalf of ASSIGNOR)

Chief Executive Officer

Title

NOTE: No witnessing, notarization or legalization is necessary. If the assignment is notarized or legalized then it will only be prima facie evidence of execution 35 USC 261. Use next page if notarization is desired.

☐ Notarization or Legalization Page Added.

JANSSEN RESEARCH FOUNDATION

April 19, 2001

Dr. Bonnie Davis
Scientific Director
Synaptech Inc.
c/o Schwartz and Salomon
225 Broadway
42nd Floor
New York, N.Y. 10007-3001

Dear Dr. Davis:

Janssen Research Foundation (JRF), a division of Janssen Pharmaceutica, Inc. which is a wholly owned subsidiary of Johnson & Johnson, hereby grants Synaptech Inc. the authority to rely upon the activities of JRF before the Regulatory Authority regarding the application for extension of patent term for U.S. patent 4,663,318 ("REMINYL").

Sincerely,

Cee A. LaPree (FOR GR)

Gaetan Rouleau
Senior Director, Regulatory Affairs

EL 712821251 7 US

administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5-1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50-300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10-2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100-600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

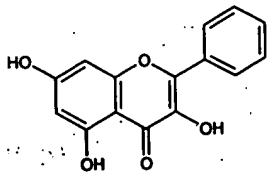
7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

* * * * *

THE MERCK INDEX

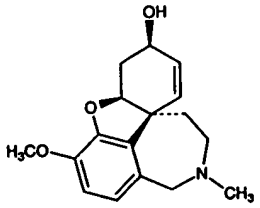
TWELFTH EDITION

Chavan, R. Robinson, *ibid.* 1933, 368. Mutagenicity studies: J. T. MacGregor, L. Jurd, *Mutat. Res.* 54, 297 (1978); J. P. Brown, P. S. Dietrich, *ibid.* 66, 223 (1979).



Yellowish needles from ethanol, mp 214-215°. Moderately sol in ethanol, ether; insol in water. Very sol in chloroform, benzene.

4357. Galanthamine. *4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol;* galantamine; lycoremine; Jilkon. $C_{17}H_{21}NO_3$; mol wt 287.36. C 71.06%, H 7.37%, N 4.87%, O 16.70%. From Caucasian snowdrops, *Galanthus woronowii* Vel., *Amaryllidaceae:* N. F. Proskurnina, A. P. Yakovleva, *J. Gen. Chem.* 22, 1899 (1952); from *Narcissus* spp: Boit *et al., Ber.* 90, 725, 2197 (1957). Structure work: Kobayashi *et al., Chem. & Ind. (London)* 1956, 177. Synthesis and stereochemistry: Barton, Kirby, *Proc. Chem. Soc.* 1960, 392; *J. Chem. Soc.* 1962, 806; Williams, Rogers, *Proc. Chem. Soc.* 1964, 357. Alternate total synthesis: Kametani *et al., J. Chem. Soc. (C)* 1971, 1043. Asymmetric synthesis of (+)- and (−)-forms from L-tyrosine: K. Shimizu *et al., Heterocycles* 8, 277 (1977). Biosynthesis studies: D. H. R. Barton *et al., J. Chem. Soc.* 1963, 4545; W. Döbke, *Heterocycles* 6, 551 (1977). Pharmacokinetics: D. Mihailova, I. Yamboliev, *Pharmacology* 32, 301 (1986). Toxicology study: S. L. Friess *et al., Toxicol. Appl. Pharmacol.* 3, 347 (1961).



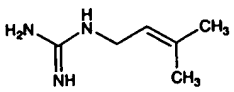
Crystals from benzene, mp 126-127°. $[\alpha]_D^{20}$ −118.8° (c = 1.378 in ethanol). Monoacidic base. Fairly sol in hot water; freely sol in alcohol, acetone, chloroform. Less sol in benzene, ether.

Hydrochloride, $C_{17}H_{21}NO_3$.HCl, crystals from water, dec 256-257°. Sparingly sol in cold, more sol in hot water. Very sparingly sol in alcohol, acetone.

Hydrobromide, $C_{17}H_{21}NO_3$.HBr, *Nivalin.* Crystals from water, dec 246-247°. $[\alpha]_D^{20}$ −93.1° (c = 0.1015 in 15 ml H_2O). LD_{50} i.v. in mice (mg/kg): 5.2 ± 0.2 (Friess).

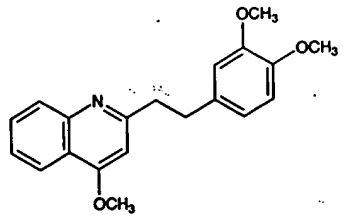
THERAP CAT: Cholinesterase inhibitor.

4358. Galegine. *(3-Methyl-2-butenyl)guanidine; N*-3,3-dimethylallylguanidine; isoamyleneguanidine. $C_6H_{13}N_3$; mol wt 127.19. C 56.66%, H 10.30%, N 33.04%. Isoprenoid guanidine deriv from seeds of *Galega officinalis* L., *Leguminosae:* Tanret, *Compt. Rend.* 158, 1182, 1426 (1914); 159, 108 (1914); Markovic, Dittertová, *Chem. Zvesti* 9, 576 (1955), *C.A.* 50, 8137d (1956). Structure: Barger, White, *Biochem. J.* 17, 827 (1923). Synthesis: Späth, Spitzy, *Ber.* 58, 2273 (1925); Babor, Jezo, *Chem. Zvesti* 8, 18 (1954), *C.A.* 49, 7495f (1955). Metabolic effects: G. Weitzel *et al., Z. Physiol. Chem.* 353, 535 (1972). Effects on mitochondria: B. Lotina *et al., Arch. Biochem. Biophys.* 159, 520 (1973). Biosynthetic study: J. Steiniger, G. Reuter, *Biochem. Physiol. Pflanz.* 166, 275 (1974). *Review:* Braun, *J. Chem. Ed.* 8, 2175 (1931).



Hygroscopic, bitter crystals. mp 60-65°. Freely sol in water or alcohol, slightly in ether. *Keep well closed.*

4359. Galipine. *2-[2-(3,4-Dimethoxyphenyl)ethyl]-4-methoxyquinoline.* $C_{20}H_{21}NO_3$; mol wt 323.39. C 74.28%, H 6.55%, N 4.33%, O 14.84%. From Angostura bark *(Cusparia trifoliata* Engl., *Rutaceae):* Körner, Böhringer, *Gazz. Chim. Ital.* 13, 363 (1883); Tröger, Kroseberg, *Arch. Pharm.* 250, 494 (1912). Synthesis: Späth, Eberstaller, *Ber.* 57, 1687 (1924); Späth, Pikl, *Ber.* 62, 2244 (1929); Schläger, Leeb, *Monatsh.* 81, 714 (1950).

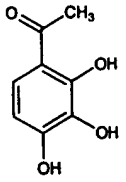


Prismatic needles from alc, mp 116°. Soluble in alcohol, benzene, chloroform, ether; slightly sol in water, petr ether. The salts are more sol than those of cusparine.

Hydrochloride tetrahydrate, $C_{20}H_{21}NO_3$.HCl.4H_2O, plates, become anhydr at 100°, mp 165°.

Methiodide, $C_{20}H_{21}NO_3$.CH_3I, yellow needles, mp 146°.

4360. Gallacetophenone. *1-(2,3,4-Trihydroxyphenyl)-ethanone; 2',3',4'-trihydroxyacetophenone;* Alizarine yellow C; C.I. 57000. $C_8H_8O_4$; mol wt 168.15. C 57.14%, H 4.80%, O 38.06%. Prepn: Hart, Woodruff, *J. Am. Chem. Soc.* 58, 1957 (1936); Campbell, Coppinger, U.S. pat. 2,686,123 (1954 to U.S. Secy. Agr.); Knowles, U.S. pat. 2,763,691 (1956 to Kodak); Price, Israelstam *J. Org. Chem.* 29, 2800 (1964).



White to brownish-gray, cryst powder, mp 173°. UV (methanol): 237, 296 nm (ε 8560, 12,500). Sol in 600 pts cold water, more in hot water; sol in alcohol, ether, sol sodium acetate.

USE: Antiseptic.

4361. Gallamine Triethiodide. *2,2',2''-[1,2,3-Benzenetriyltris(oxy)]tris[N,N,N-triethylethanaminium] triiodide; [v-phenenyltris(oxyethylene)]tris[triethylammonium triiodide];* 1,2,3-tris(2-triethylammonium ethoxy)benzene triiodide; 1,2,3-tris(2-diethylaminoethoxy)benzene tris(ethiodide); tri(β-diethylaminoethoxy)-1,2,3-benzene triiodide); tri(β-diethylaminoethyl ether) tris(ethylate; pyrogallol 1,2,3-(diethylaminoethyl ether) tris(yl iodide); benzcurine iodide; RP-3697; F-2559; Tricuronium; Retensin; Relaxan; Flaxedil. $C_{30}H_{60}I_3N_3O_3$; mol wt 891. C 40.42%, H 6.78%, I 42.70%, N 4.71%, O 5.38%. Curing properties: D. Bovet *et al., Compt. Rend.* 225 (1947); F. Depierre, *ibid.* 956. Prepn: E. Fourneau, pat. 2,544,076 (1951 to Rhone-Poulenc). Comparative clinical pharmacokinetics: W. Buzello, S. Agoston, *Anaesthesist* 27, 313 (1978). Mode of action: D. Colquhoun, Sheridan, *Brit. J. Pharmacol.* 66, 78 (1979); *eidem, Proc. Roy. Soc. London, Ser. B* 211, 181 (1981). Effects in mammalian and amphibian nerve fibers: K. J. Smith, Schauf, *Science* 212, 1170 (1981).

administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5-1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50-300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10-2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100-600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

* * * * *

United States Patent [19]

Davis

[11] **Patent Number: 4,663,318**

[45] **Date of Patent: May 5, 1987**

[54] **METHOD OF TREATING ALZHEIMER'S DISEASE**

[76] Inventor: **Bonnie Davis, 17 Seacrest Dr., Huntington, N.Y. 11743**

[21] Appl. No.: **819,141**

[22] Filed: **Jan. 15, 1986**

[51] Int. Cl.[4] **A61K 31/55**

[52] U.S. Cl. **514/215**

[58] Field of Search 514/215

[56] **References Cited**

PUBLICATIONS

Chem. Abst. (81)-72615z (1974).

Chem. Abst. (86)-115157z (1977).

Horshenson et al. J. Med. Chem. vol. 29, No. 7, 7/86, pp. 1125-1130.

Kendall et al., J. Chem. & Hospital Pharmacol., (1985) 10-327-330.

S. Chaplygina et al., J. of Highest Nervous Activity vol. XXIV 1976 Issue 5, pp. 1-4.

Krause, J. of Highest Nervous Activity, vol. XXII, 1974, Issue 4.

Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Ladas & Parry

[57] **ABSTRACT**

Alzheimer's disease may be treated with galanthamine.

7 Claims, No Drawings

METHOD OF TREATING ALZHEIMER'S DISEASE

GENERAL FIELD OF THE INVENTION

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

BACKGROUND ART

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163-8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta Anesth. Scand. 24:166-168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615Z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-1093, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

SUMMARY OF THE INVENTION

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

Galanthamine can be administered in any convenient chemical or physcial form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1-50 mg/ml more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, typically 20-30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine by injection are in the range 5-1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5-5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50-300 mg per day to a patient of a body weight of 40-100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100-600 mg per day. In preparing such tablets or capsules, standard tablet or capsulemaking techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft galatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacyin Alzheimer's disease. Haroutunian, V, Kanof P, Davis, K.L: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. Life Sciences 37:945-952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5 mg/5 ml and 25 mg/5 ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. In such cases, it may be desirable to

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ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,663,318	273	245	----	06/819,141	05/05/87	01/15/86	04	YES	PAID
2	4,385,073	171	495	----	06/362,234	05/24/83	03/26/82	08	NO	PAID
3	4,666,940	173	490	----	06/767,476	05/19/87	08/20/85	04	NO	PAID

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ITM NBR	ATTY DKT NUMBER
1	U 5631
2	IFF-2741
3	U 5517

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ITM	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
3R	4,663,318	185	3160	----	06/819,141	05/05/87	01/15/86	12	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

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